

REVIEW

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Targeting tumor-necrosis factor receptor pathways for tumor immunotherapy

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Abstract

With the success of ipilimumab and promise of programmed death-1 pathway-targeted agents, the field of tumor immunotherapy is expanding rapidly. Newer targets for clinical development include select members of the tumor necrosis factor receptor (TNFR) family. Agonist antibodies to these co-stimulatory molecules target both T and B cells, modulating T-cell activation and enhancing immune responses. *In vitro* and *in vivo* preclinical data have provided the basis for continued development of 4-1BB, OX40, glucocorticoid-induced TNFR-related gene, herpes virus entry mediator, and CD27 as potential therapies for patients with cancer. In this review, we summarize the immune response to tumors, consider preclinical and early clinical data on select TNFR family members, discuss potential translational challenges and suggest possible combination therapies with the aim of inducing durable antitumor responses.

Keywords: Cancer, Immunotherapy, 4-1BB, OX40, GITR

Introduction

After nearly a century of skepticism regarding the efficacy of immunotherapy in cancer, a resurgence has begun that is driven primarily by the success of ipilimumab [1]. The immune-mediated mechanism of action and resultant antitumor activity of ipilimumab lend support to the notion that tumors are under immune surveillance. Moreover, the concept of “immuno-editing” suggests that the pressure exerted on tumors by the immune system shapes or “edits” tumor cells, allowing their escape from immune elimination [2]. Briefly, the immune system is capable of eliminating malignant cells during initial transformation. As tumors grow, an “equilibrium” is reached where immune tumor growth is matched by immune-mediated tumor destruction. Eventually, malignant cells either accumulate mutations, making them non-immunogenic, or immunosuppressive pathways become activated, allowing the tumor to escape immune recognition [2-5]. It now appears that targeting immunomodulatory mechanisms can tip the balance from escape back toward elimination. In addition to ipilimumab and other co-inhibitory

checkpoints (i.e., programmed death-1 [PD-1]), research into the stimulation of T cell responses via agonist therapies has opened another therapeutic possibility. This review will focus on the rationale for targeting co-stimulatory pathways in T cells, summarize agents in development, and offer possible treatment strategies using these agents in combination with other immunotherapies.

Review

The host response to tumors has been well described [6-9]. However, tumors have developed ways to escape this response via a number of mechanisms; these have been extensively reviewed previously [6-8,10]. The accumulation of suppressive cells and an inhibitory cytokine milieu in and around the tumor can form an immunosuppressive environment that prevents successful T cell-mediated destruction of malignant cells [11]. The goal of many immunotherapies is to help the immune system overcome the mechanisms that tumors employ to evade destruction.

Targeting immune “checkpoint” pathways

Upon initial activation by antigen-presenting cells (APCs), tumor-specific T cells receive essential co-stimulation through binding of CD28 to CD80/86 on activated APCs. However, the CD28-CD80/86 pathway is antagonized by

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cytotoxic T lymphocyte antigen-4 (CTLA-4; CD152), one of the first co-inhibitory checkpoints that self-limit responses. CTLA-4 competes with CD28 for CD80/86 binding and has a much greater affinity than CD28 for CD80; CTLA-4 signaling decreases the magnitude of early T-cell activation, expansion, and function [12-14]. Ipilimumab blocks CTLA-4 antagonism of CD28 and was the first agent to demonstrate an overall survival benefit for patients with metastatic melanoma [1,15]. The ability of CTLA-4 blockade to enhance tumor immunity may be because most tumor antigens are modified self-antigens or mutated unique antigens against which T cell cytotoxic function is believed to be relatively poor. Therefore, by releasing this first brake on immune activation, ipilimumab allows the generation of a more effective immune response [16].

Subsequent to CTLA-4, PD-1 was also shown to regulate the immune response. PD-1 interacts with B7-homolog 1 (B7-H1 or programmed death receptor-1 ligand1 [PD-L1]) and B7-DC (PD-L2) on APCs and tumor cells. Ligation of PD-1 by either of its ligands downregulates T-cell receptor (TCR) signaling and abrogates stimulatory cytokine production [17,18]. Moreover, PD-1 upregulation on effector T cells identifies T cells with an exhausted phenotype that cannot maintain polyfunctional cytokine production [19]. Although the evaluation of PD-1/PD-L1-targeted therapies is at an early stage, they are showing promising results. Evaluation of the anti-PD-1 antibody nivolumab in more than 300 patients in a phase I trial, showed antitumor activity in patients with non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), and melanoma, and an encouraging safety profile [20,21]. Combination of nivolumab with ipilimumab has also demonstrated a potentially synergistic effect in a recent phase I combination study for patients with advanced melanoma [22]. Phase III trials in these tumors are ongoing. The anti-PD-1 antibody

CT-011 has shown activity in a small phase I trial of patients with various hematological malignancies [23]. Data with other anti-PD-1 and anti-PD-L1 antibodies and fusion proteins are becoming available [24-27].

TNFR superfamily costimulatory molecules

In addition to blocking co-inhibitory pathways, activating co-stimulatory pathways to potentiate antitumor immune responses is a promising approach. Members of the tumor necrosis factor receptor superfamily (TNFRsf) include several co-stimulatory proteins with key roles in B and T cell development, survival, immune activation, and antitumor immune responses [28]. These co-stimulatory TNFRsf members lack death domains, enabling them to enhance activation and proinflammatory cascades [29], making them attractive therapeutic targets (Table 1). Recent clinical success with checkpoint inhibitors has provided the rationale for investigating agonism of 4-1BB (CD137), OX40, glucocorticoid-induced TNFR-related gene (GITR), herpes virus entry mediator (HVEM), and CD27 in order to extend clinical benefit to more patients.

4-1BB (CD137)

4-1BB is a molecule with profound effects on T-cell proliferation and CD8⁺ T-cell function [30-32]. It is primarily present on activated but not resting T cells, activated natural killer (NK) cells, and natural killer T (NKT) cells. It is expressed constitutively on certain populations of dendritic cells (DCs) and regulatory T cells (Tregs) [33-36]; 4-1BB expression is upregulated on monocytes upon activation [35]. Stimulation of 4-1BB by either its natural ligand, 4-1BBL, or by agonist antibodies enhances the activation of various immune cells, including T cells, DC (upregulation of B7 molecules and immunostimulatory cytokine production), monocytes, and neutrophils (proinflammatory cytokine secretion), and induces a

Table 1 TNFR-targeted agents in development

TNF receptor molecule	Name	Description	Sponsor	Phase in cancer patients
4-1BB (CD137)	CART19 cells	T cells transduced with antibody against CD19 linked to the intracellular signaling domains of 4-1BB and CD3-zeta	University of Pennsylvania and others	II
	Urelumab	Fully human anti-CD137 agonist monoclonal antibody	Bristol Myers-Squibb	I
OX40		Mouse monoclonal anti-OX40 agonist antibody	Providence Health & Services and others	II
		Humanized antibody against OX40		Preclinical
GITR	hFcILZOX40L	Recombinant human Fc:OX40L fusion protein	Providence Portland Medical Center	Preclinical
	TRX518	Humanized anti-GITR agonist monoclonal antibody	GITR, Inc.	I
CD27	GITRL RNA DC	GITRL-expressing DCs	Duke University	I
	CDX-1127	Fully human anti-CD27 agonist monoclonal antibody	Celldex Therapeutics	I

Abbreviation: DCs Dendritic Cells, GITR Glucocorticoid-Induced TNFR-Related Gene, GITRL GITR Ligand, TNF Tumor-Necrosis Factor, TNFR Tumor-Necrosis Factor Receptor.

spectrum of effects on B and NK cells [35,36]. 4-1BB signaling can co-stimulate T cells in a CD28-independent manner [37], protect tumor-infiltrating lymphocytes (TILs) from activation-induced cell death (AICD) via upregulation of antiapoptotic pathways [38,39], and enhance cytotoxic T lymphocyte (CTL) survival and cytolytic activity [40].

Preclinical data show that targeting 4-1BB with an agonist antibody can promote tumor control in numerous pre-clinical models, and is often associated with increased CTL effector capability [36,41-43]. The effects of pairing agonist anti-4-1BB antibodies with other therapies have also been investigated. Anti-4-1BB antibody administered with adoptive T-cell therapy resulted in survival and resistance to rechallenge in 80% of mice bearing established thymomas [44]. Combining anti-4-1BB with an agonist anti-CD40 plus a blocking antibody against DR5, a receptor for TRAIL (a strategy termed “trimab”), had activity against multiple transplanted tumors in mice [45]. Adding anti-CTLA-4 further increased the potency of this approach, resulting in ~80% tumor rejection of established mammary 4 T1 tumors in mice [46]. Combining CTLA-4 blockade and 4-1BB co-stimulation with a granulocyte-macrophage colony-stimulating factor (GM-CSF)-secreting melanoma vaccine greatly improved tumor eradication and promoted survival compared with vaccine plus either agent [47]. Combination treatment increased proliferation and tumor infiltration by both CD4⁺ and CD8⁺ T cells, and intratumor inflammatory cytokine production. Likewise, a 4-1BBL-expressing RM-1 cell vaccine used with CTLA-4 blockade in mice bearing RM-1 prostate tumors improved survival compared with mice treated with monotherapy [48]. These data suggest that concurrent manipulation of the CTLA-4 and 4-1BB signaling pathways merits clinical evaluation.

Other combinations have also been investigated. Kohrt and colleagues showed human trastuzumab-activated NK cells had improved cytotoxicity against breast cancer cells when stimulated with an agonist 4-1BB antibody [49]. Agonistic anti-4-1BB antibodies also had antitumor activity when given together with radiation therapy in murine breast and lung cancer models and when combined with anti-PD-1 plus radiotherapy [50,51]. Finally, targeting 4-1BB with intratumoral interferon- α therapy or DC-based vaccination also produced significant antitumor responses and/or improved survival [52,53].

Against this background, agonist 4-1BB therapy with urelumab (BMS-663513) was investigated in patients with melanoma, RCC, and ovarian cancer. Although some antitumor activity was observed during a phase I trial, safety concerns halted development [54,55]. Development has recently restarted using urelumab at a lower dose in combination with other agents (NCT01471210 and NCT01775631, clinicaltrials.gov).

A different approach to utilizing the immune-potentiating properties of 4-1BB has been explored in the context of chimeric antigen receptor (CAR)-transduced T cells. Expressing an antibody with specificity for the B cell antigen CD19 linked to the intracellular signaling domains of 4-1BB and CD3- ζ enhanced the survival and effector functions provided by transduced T cells directed against tumor cells. T cells with this modified CAR (termed “CART19” cells) infused into a patient with refractory chronic lymphocytic leukemia (CLL) induced complete disease remission that was ongoing for more than 10 months [56]. Clinical studies of CART19 cells in patients with various B cell leukemias and lymphomas are ongoing (clinicaltrials.gov).

OX40 (CD134)

OX40 (TNR4) [57] is similar to 4-1BB and GITR, and engagement promotes T-cell activation, survival, proliferation, and cytokine production [58-62]. OX40 is primarily expressed on activated CD4⁺ T cells 24–48 hours after activation, and on CD8⁺ T cells, neutrophils, dendritic cells, and Tregs [60,63]. The natural ligand of OX40, OX40 ligand (OX40L), is most common on APCs, and is also found on activated T cells. OX40 expression is induced by TCR stimulation, but co-stimulation through other molecules, such as CD28, or exposure to certain cytokines can further upregulate expression [64]. While OX40 has a key role in the development and function of Tregs, engagement of OX40 with an agonist antibody can also deactivate the suppressive function of Tregs [63,65-69].

OX40 agonism has been investigated in multiple tumor models. As a monotherapy, it delayed tumor growth *in vivo* and promoted the rejection of various tumors [60,62,70]. OX40-dependent antitumor immunity required both CD4⁺ and CD8⁺ T cells, and a significant proportion of treated mice remained tumor-free and resistant to rechallenge, supporting the notion that OX40 engagement promotes memory [71]. Combination approaches aimed at improving the efficacy of OX40 engagement have been explored. Combinations of anti-OX40 with fractionated radiotherapy, interleukin (IL)-12 and anti-4-1BB, anti-CTLA-4 and CpG oligonucleotides, anti-CD25 and anti-CTLA-4 with adoptive cell transfer, transforming growth factor (TGF)- β inhibition, or IL-2 improved antitumor responses, tumor rejection, long-term survival, and/or resistance to tumor rechallenge in mice bearing various cancers [64,71-75]. We have shown that combining anti-OX40 with cyclophosphamide led to the regression of the poorly immunogenic B16 murine melanoma and was associated with fewer intratumoral Tregs, leading to a favorable effector/Treg cell ratio within the tumor microenvironment [76]. Adoptive transfer of melanoma specific CD4⁺ T cells together with OX40 and cyclophosphamide eliminated even more advanced melanomas. This

combination triggered cytolytic activity in the transferred CD4⁺ T cells, a phenomenon largely responsible for the potency of this combination [76].

In the first-in-human clinical trial, 30 patients with solid tumors received a murine anti-human OX40 monoclonal antibody at doses from 0.1 through 2 mg/kg; the maximum tolerated dose was not identified, and some patients had an objective response after one dose [77]. Humanized OX40 antibodies and a fully human OX40L:IgG fusion protein have been developed [60,78,79]. Phase II clinical trials evaluating OX40 agonists with stereotactic radiation and/or cyclophosphamide in patients with multiple tumor types are ongoing (NCT01642290, NCT01303705).

GITR (CD357)

GITR is expressed at low levels on resting CD4⁺ and CD8⁺ T cells, is upregulated after 24–72 hours of stimulation, and remains expressed for several days [80–82]. In contrast to effector T cells, Tregs constitutively express GITR. GITR has also been observed on DC, monocytes, and NK cells. Similar to OX40 and 4-1BB, ligation provides co-stimulatory signals that enhance T-cell proliferation and effector function, and protect T cells from AICD [81,82]. GITR ligand (GITRL) is highly expressed on activated APCs and endothelial cells (ECs). Interestingly, while the role of GITRL on APCs appears primarily to provide costimulation, it was recently shown that GITRL/GITR interactions on EC may be important for triggering leukocyte adhesion and transmigration [83]. Although human and mouse GITR have similar characteristics, unlike most TNFR family members, murine GITR exists as a dimer instead of a trimer [84,85]. How this difference relates to the biological functions of mouse and human GITR is unknown.

Reports showing GITR ligation can break self-tolerance and abrogate T-cell suppression by Tregs identify it as a target for cancer immunotherapy [86,87]. Our laboratory was the first to demonstrate that an agonist anti-GITR antibody, the rat monoclonal DTA-1, could protect mice from B16 tumor rechallenge and that treatment induced rejection of small, established B16 tumors [88,89]. Stimulation of GITR also cured established sarcomas, induced long-lasting memory, and had activity in other mouse models [82,90]. GITRL manipulation has also been explored. Mice bearing GITRL-expressing tumors had improved CTL effector function and peritumoral injection of a GITRL vaccine slowed the growth of established tumors [91].

Multiple mechanisms appear to contribute to the antitumor effects of GITR modulation. We have demonstrated that DTA-1 administration impaired intratumoral Treg expression of FoxP3, resulting in a loss of Treg lineage stability and abrogation of intratumor Treg suppressive function [92]. This led to a higher effector T cell (Teff):

Treg ratio and improved antitumor CTL function [88]. Additionally, Côté and colleagues found that DTA-1 treatment enhanced the development of high-avidity CTL responses to tumor-associated antigens in a mouse melanoma model [93]. Recent reports show that DTA-1 can cause depletion of intratumoral Tregs through interactions between the antibody and activating Fc_YRs on myeloid cells [94]. Because of differences in tumor models and underlying treatment conditions, it is unclear if one of these mechanisms is dominant or if all play a role in GITR agonist immunotherapy. The exact contribution of each will require further investigation.

GITR agonism (either via DTA-1 or GITRL fusion protein) has been successfully combined with other immunotherapies, including DNA- or DC-based vaccines [93,95–97]. Response to DTA-1 in mice bearing fibrosarcoma or colorectal carcinoma improved in combination with adoptive T-cell transfer or an antagonistic anti-CTLA-4 antibody [90,98,99]. Pruitt and colleagues saw improvements in antitumor immunity when a melanoma DC vaccine was combined with DCs expressing anti-CTLA-4 and anti-GITR mRNA [100].

While most reports show GITR-GITRL interactions are co-stimulatory to T cells, data regarding the immune-stimulating potential of GITR on non-T-cell subsets, particularly NK cells, are conflicting. Human leukemia cell expression of GITR-L interferes with NK cell-mediated immunity through reverse signaling, which causes tumor production of suppressive cytokines, downregulation of co-stimulatory molecules, and evasion from immune detection [101,102]. Nonetheless, in collaboration with Ludwig Cancer Research, Cancer Research Institute, and GITR, Inc. (Cambridge, MA, USA), we initiated a phase I trial (NCT01239134) of the humanized anti-GITR antibody TRX518 [103]. A trial examining the effects of GITRL-expressing DCs (with or without DC expressing anti-CTLA-4) plus a DC tumor vaccine in patients with melanoma is also ongoing (NCT01216436).

HVEM (CD270)

HVEM, another member of the TNFR superfamily [104], has multiple binding partners and various downstream effects that can positively and negatively modulate T-cell activation [105]. HVEM expression kinetics are the opposite of 4-1BB, OX40, and GITR: HVEM is highly expressed on resting T cells but downregulated upon activation. When cells return to less-activated states, HVEM expression is restored. There is significant HVEM expression on naive and memory, but not activated, B cells. Other immune cells, including Tregs, NK cells, monocytes, and immature DCs, also express HVEM. There are at least four natural ligands for HVEM: the inhibitory Ig-related molecules CD160 and B and T lymphocyte attenuator (BTLA; capable of bidirectional signaling)

and the stimulatory TNF-related cytokines LIGHT and lymphotoxin-alpha [106-109]. LIGHT is expressed upon T and B cell activation and on monocytes and immature DCs. BTLA is found on various lymphoid and myeloid cells, with particularly high expression on B cells and plasmacytoid DCs. CD160, by contrast, is observed only on subsets of T and NK cells [105]. While binding of LIGHT or lymphotoxin- α to HVEM triggers T and B cell stimulation and APC maturation and differentiation, CD160 or BTLA binding to HVEM on T or B cells has the reverse effect, inhibiting T and B cell activation.

Studies have explored the potential of the HVEM pathway as a therapeutic target. Murine P815 mastocytoma cells engineered to express the single-chain variable fragment (scFv) of an anti-HVEM agonistic monoclonal antibody stimulated proliferation and cytokine production in co-cultured T cells [110]. Expression of anti-HVEM scFv *in vivo* resulted in T-cell-dependent tumor rejection (in 80% of treated mice) and a lasting memory response. Combination of the anti-HVEM scFv-expressing tumor vaccine with anti-4-1BB monoclonal antibody therapy synergized to induce regression of more established tumors, leading to survival and memory responses not seen with either agent alone [111]. In melanoma patients, tumor-specific T cells were found to express BTLA concurrent with HVEM [108,109]. Fourcade and colleagues tested the significance of this expression, showing that BTLA blockade enhanced the proliferation and antitumor activity of melanoma-specific CD8 $^{+}$ T cells [109]. Approaches to mono- or combination therapy are presented in the review by Pasero and colleagues [105]. However, manipulating the HVEM signaling pathway(s) provides a significant challenge, requiring agents that precisely induce HVEM-related immunostimulatory effects or block HVEM-related immunosuppressive effects.

CD27

CD27 has a key role in the generation of immunological memory via effects on T-cell expansion and survival, and B cell development [112-114]. CD27 is constitutively expressed on conventional T cells (including populations of Tregs) and, like other members of the TNFRsf, is up-regulated upon activation [115]. Expression of CD27 on human Tregs correlates with FoxP3 expression and suppressive functionality [116,117]. CD27 is also expressed on subsets of B cells, most strikingly on plasma cells, for which it is a broadly accepted marker [118]. CD70, the natural ligand for CD27, is transiently expressed on activated APCs and T cells [119]. Ligation of CD27 by CD70 has stimulatory effects on T-cell proliferation, expansion, and survival dependent upon IL-2 autocrine signaling [120].

Triggering CD27 signaling in CAR-transduced T cells can enhance effector function, survival, and improve

antitumor activity in a xenograft mouse model of ovarian cancer [121]. Constitutive CD70 expression on tumors or DCs improved antitumor immunity in murine lymphoma models, enhancing NK-mediated rejection of class-1 deficient tumor cells via perforin- and IFN- γ -dependent mechanisms [122]. CD70 expression also leads to generation of memory T-cell response to secondary tumor challenge. Conversely, intact CD27/CD70 signaling has been associated with decreased antitumor immune responses and an increased intratumoral Tregs (potentially due to improved Treg resistance to apoptosis and increased IL-2 secretion by effector T cells). Compared with wild-type mice, tumors in CD27-deficient mice had decreased vascularization and slower growth [123]. Furthermore, wild-type mice treated with an anti-CD27 blocking antibody had fewer Tregs and slower tumor growth than untreated mice. In this setting, Tregs were critical mediators of CD27-dependent effects on tumor growth. Schurch and colleagues similarly demonstrated that CD27 triggering by CD70 ligation in chronic myelogenous leukemia stem cells accelerated disease progression and was associated with activation of the Wnt pathway [124]. Such data complicate the consideration of CD27 as a target for tumor immunotherapy. The effects of CD27 pathway triggering may depend upon the environment in which the stimulus is delivered—within the tumor microenvironment or in peripheral lymphoid tissues—as well as length of exposure to stimulating agents.

A fully human monoclonal CD27 agonist antibody, CDX-1127 (Celldex Therapeutics, Inc. Needham, MA, USA), is being evaluated in a phase I clinical trial in select hematological and solid tumors [125]. Preclinical experiments with a mouse homologue showed delayed human hematological tumor growth in xenograft mouse models and murine tumor growth in immunocompetent mice [126]. Again, similar to HVEM, continued clinical development of CD27-related agents will require teasing apart the multiple inhibitory and co-stimulatory mechanisms that target multiple cell populations, and precise triggering of certain molecules in select environments to avoid exaggerating tumor-induced immunosuppression. Since Tregs appear to be a critical target of CD27 agonism, perhaps prior Treg depletion may be appropriate.

Conclusions

The success of cancer immunotherapy with agonist antibodies may vary according to tumor type, since the expression of the target molecules can differ across tumors (for example, the expression of HVEM in certain leukemias and lymphomas). Although a multifactorial approach to cancer therapy is attractive [127], the potential risk of autoimmune reactions and bystander tissue damage in the setting of immunostimulation should not be underestimated. The well-documented phase I

study of the anti-CD28 monoclonal antibody TGN1412, in which six healthy volunteers suffered massive cytokine release and major organ damage, emphasized the need for extreme caution in trial design and execution when investigating immune activators [128]. It should be noted, however, that CD28 is constitutively expressed on T cells, whereas most of the TNFRsf members are up-regulated upon activation. Therefore, targeting TNFRsf members might have more restricted downstream effects, including a more defined toxicity profile.

Targeting the co-stimulatory TNFRsf shows promise for the treatment of cancer. Although there have been life-threatening side effects with some agonist antibodies, there is obvious clinical activity, emphasizing the need for careful titration and dosing. From this perspective, it may not be necessary to “press on the gas” constantly if agonist antibodies are administered with a checkpoint blocker (i.e., anti-PD-1, anti-CTLA-4) to “remove the brake”.

The mechanisms of immune evasion are not the same for each patient’s tumor (even of the same tumor type) and as such, monotherapies may not achieve sufficient potency. Combinatorial approaches, which include targeting TNFRsf, show promise in preclinical studies. Thus, combination with chemotherapy or irradiation, which can induce immunogenic cell death and stimulate antitumor T cells, is a rational. Additionally, combining anti-TNFRsf antibodies with small molecule inhibitors should be considered. Although clinical studies of TNFRsf agonists are at an early stage, careful development may see additional therapies brought to patients who most need them most.

Abbreviations

AICD: Activation-induced cell death; APCs: Antigen-presenting cells; B7-H1: B7-homolog 1; BTLA: B and T lymphocyte attenuator; CAR: Chimeric antigen receptor; CD137: 4-1BB; CLL: Chronic lymphocytic leukemia; CTL: Cytotoxic T lymphocyte; CTLA-4: Cytotoxic T lymphocyte antigen-4; DCs: Dendritic cells; ECs: Endothelial cells; GITR: Glucocorticoid-induced TNFR-related gene; GITRL: GITR ligand; GM-CSF: Granulocyte-macrophage colony-stimulating factor; HVEM: Herpes virus entry mediator; IL: Interleukin; MDSC: Myeloid-derived suppressor cells; NK: Natural killer; NKT: Natural killer T cells; NSCLC: Non-small cell lung cancer; OX40L: OX40 ligand; PD-1: Programmed death receptor-1; PD-L1/2: Programmed death receptor-1 ligand1/2; RCC: Renal cell carcinoma; scFv: Single-chain variable fragment; TCR: T-cell receptor; Teff: Effector T cell; TILs: Tumor-infiltrating lymphocytes; TNF: Tumor-necrosis factor; TNFR: Tumor-necrosis factor receptor; TNFRsf: Tumor necrosis factor receptor superfamily; Treg: Regulatory T cell.

Competing interests

DS and DH declare no competing interest. JW discloses that he is a paid consultant for Medimmune and Bristol-Myers Squibb.

Authors' contributions

DS, DH and JW contributed equally to the development of this manuscript. All authors read and approved the final manuscript.

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